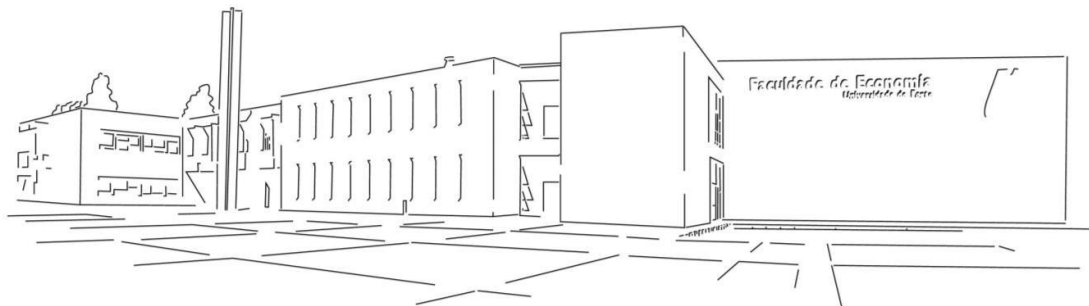


Early Stage Biopharmaceutical R&D Financing: A Real Options Approach.

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Biography

Anselmo Manuel Silva Gomes was born in Vila Nova de Gaia, on November 27, 1990. After completing high school there, he moved to Porto in 2008 to pursue his studies in Economics, at FEP School of Economics and Management.

His interest in financial markets led him to continue his academic journey again at FEP School of Economics and Management, but this time to enroll on the Master in Finance. It is to obtain this degree that this dissertation has been developed under the supervision of Prof. Dr. Paulo Pereira.

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Abstract: This work presents an overview of the biopharmaceutical sector, its process of research and development and the methods utilized by the sector to maintain and expand their drug pipelines. We will pick on the Mega fund structure used by Lo et al. (2014), and apply a real options to it, comparing our results, and afterwards present the benefits that the introduction of a State Subsidy could have on the decision to implement the project. Concluding with an analysis from the point of view of the state in order to find if the attribution of such a subsidy could be considered optimal.

Abstrato: Este trabalho apresenta uma visão geral do setor biofarmacêutico, do seu processo de *research and development* e dos métodos utilizados pelo setor para manter e expandir as suas *drug pipelines*. Partindo da estrutura de *Mega Fund* usada em Lo et al. (2014), e posteriormente aplicando a metodologia de opções reais, vamos comparar os nossos resultados e, posteriormente, apresentar os benefícios que a introdução de um subsídio do Estado poderia ter sobre a decisão de implementar o projeto. Concluindo com uma análise do ponto de vista do Estado, no sentido de descobrir se a atribuição de tal subsídio poderia ser considerado ótimo.

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Chapter 1 - Introduction

The biopharmaceutical sector is the sector with the highest ratio of research and development (R&D) investment to net sales. The introduction of a new drug in the market is the way through which companies remain competitive (Banerjee & Nayak 2015). Being the last step of a long process of R&D which requires large amounts of investment, it has been increasing for over 50 years creating a high burden on companies which in the last couple of decades have also been faced with other issues, such as the patent-cliff and increasing global pressure for drug price control.

The completion of the Human Genome Project in 2003 HGP was considered to be a monumental discovery for the Biopharmaceutical sector¹, but it also created the need for the sector to change its practices, in order to adapt to new genomic technologies. According to 'The Fruits of Genomics' this period of adaptation would lead to a decade of struggle with the new biological targets that would result in lower productivity, higher failure rates, skyrocketing costs and potential lower stock returns.

The biotechnology sector took advantage of the possibilities offered by the discovery, marking the start of stable and high growth period that extends to the present. In contrast the pharmaceutical sector between the early 2000 up to 2012 experienced a period where the sector went on a negative trend destroying shareholder value.

As companies are faced with the need for continued renovation of their drug pipelines, they are not simply focusing on simply expanding their own in-house R&D, relying also on other alternatives like mergers and acquisitions (M&A) and strategic alliances. Besides public and private equity, which are among the largest and best known financing sources in the sector (Schiff & Murray 2004) there are other financing vehicles, such as, special purpose entities (SPE), private investments in public equities, bridge financing, and royalty financing, which can help companies in the sector to finance themselves through the long and expensive process of R&D.

¹ Lehman Brothers Equity Research: Global Life Sciences, "The Fruits of Genomics," Lehman Brothers Equity Research, New York (January 30, 2001).

These new investment are starting to close the investment gap of R&D, however until now they only are financing the lower risk, late stage and FDA approval pending drugs (Lo *et al.* 2014).

The investment in early stage is still considered too risky to be financed by standard means. Fernandez *et al.* 2012 proposed a structure that could address the funding gap of early stage R&D, called Mega Fund. The Mega Fund will be able to mitigate the high risk involved in early stage R&D throw diversifying its portfolio, by acquiring economic rights in a large amount of early stage drug compounds, which will lower the overall risk of the Mega Fund in such a way that enables it to issue securities backed by those early stage R&D drug compounds to which he called ‘research-backed obligation’ (RBO).

The size required to properly mitigate the risk may vary from case to case, depending on the area of research and the correspondent time probability of success and correlation among the drug compounds.

When the methodology was applied to the case of the Alzheimer disease (AD) it was found that due to the increased development costs, increased development period and lower availability of compounds an AD Mega Fund would not be viable. Despite these facts, the benefits arising from the discovery of new drugs in this area according to Lo *et al.* (2014) has the possibility to generate cost savings that could possibly overcome the problems that AD R&D faces and proposed four different approaches for the government to take in order to accelerate the development of AD therapeutics: by providing guarantees for the debt of an AD Mega Fund; by starting the patent clock upon commercialization rather than invention; by increasing the duration of patent protection from 20 to 30 years for AD therapeutics that meet a sufficiently high efficacy threshold; or by providing more funding for basic research on neurodegenerative diseases.

On this dissertation we will present a different approach than the ones proposed in order to evaluate the performance of an AD Mega Fund, following a real options approach, starting with the calculations of the optimal timing for investment of the AD Mega Fund according to the parameters used Lo *et al.* (2014), were our results coincided almost entirely with the ones of Lo *et al.* (2014), presenting afterwards a different analysis where we test the effect of the introduction of a state subsidy with the aim of stimulating

the immediate start of the Mega Fund, and concluding with an analysis from the state point of view, to test if the attribution of such a subsidy is in their interest, where the results suggest that in almost all scenarios with a 20 or 30 year horizon, the decision to give the subsidy should be taken.

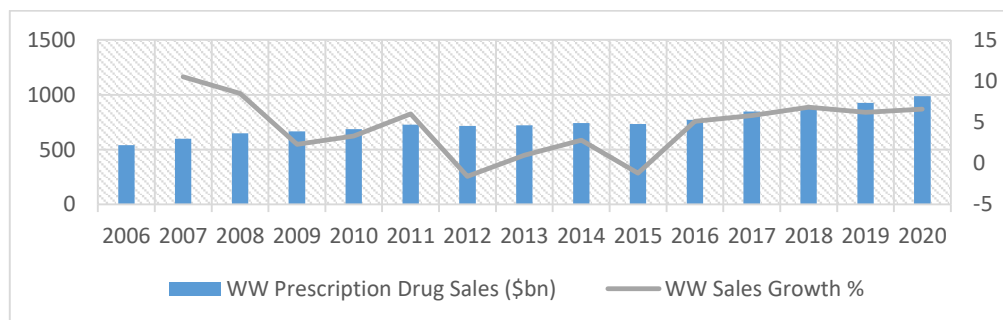
The structure of this dissertation is as follows: in chapter 2 we will make a presentation of the relevant literature review, starting with a presentation of the biopharmaceutical sector, the steps that compose a general R&D process of a drug compound and finally present some strategies used by the Biopharmaceutical companies to renew and finance their drug pipelines; in Chapter 3 we start by presenting the base intuition presented by (Lo *et al.* 2014) for the creation of an AD Mega Fund which is followed by our adaptation using a real option model, where we test if the Mega Fund as proposed by (Lo *et al.* 2014) is suitable to enter the market by calculating the value of its investment opportunity (IO) and the option to defer (OD) for each scenario. Afterwards we propose the introduction of an state subsidy at $t = 0$, which will reduce the capital investment required by the Mega Fund in such a way that the decision to enter the market is always optimal at $t = 0$, finally we propose an analysis of that subsidy to test if the attribution of such a subsidy at $t = 0$ should be in the interest of the state, by setting the capital requirement to the amount of the subsidy calculated previously for each scenario and the value of the project to the present value of the cost savings in Medicaid and Medicare, that are expected to be generated by the Mega Fund through its activity; in chapter 4 we expose the results from our calculations and analyze them, comparing to the findings from Lo *et al.*, 2014; finally on chapter 5 we present our conclusions.

Chapter 2 – Literature Review

2.1 - Biopharmaceutical Sector

The biopharmaceutical sector performance is highly correlated with healthcare spending levels and the economic strength amongst countries². The sector has endured well the recent economic recession, having the overall worldwide sales (Figure 1) kept a growing tendency since 2006 with the exception of 2012 and 2015 where a decrease in overall sales was observed. It is expected that from 2014 to 2020 the sector will achieve an annual compound growth rate of 4.8%. This growth is expected to be achieved mainly in the emerging market economies since the US and European growth is stagnating, which will expose companies to varying types and levels of economic uncertainty³.

Figure 1 – Worldwide Prescription drug sales and growth.



Source: EvaluatePharma, (2015), World preview 2015, outlook to 2020.

Demographic factors⁴ such as the aging of the population and increased life expectancy are helping the proliferation of chronic diseases in developed and non-developed countries, and will lead to increasing demand for drugs and treatments in the future.

² Deloitte, (2015) Global life sciences outlook. In: Adapting in an era of transformation

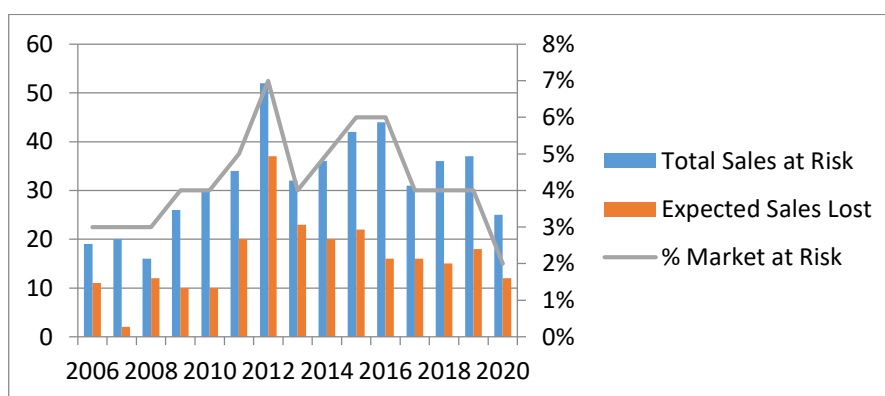
³ EvaluatePharma, (2015), World preview 2015, outlook to 2020

⁴ Deloitte, (2016). Global life science outlook. In: Moving forward with cautious optimism

The sector is facing a global trend of reform-driven drug price control⁵, where biopharmaceutical companies are facing increasing pressure from public and private payers to control costs, justify the cost of their products based on their effectiveness compared to similar products, and government incentives for the use of generics (Gautam & Pan 2016).

Another factor that is pressuring companies is the patent-cliff (Paul *et al.*, 2014), characterized by a decline in revenues due to the expiration of the drug patents, which could be used as an explanation to the decline in the sales growth observed (Figure 1). In the biopharmaceutical sector, patent life plays a crucial role, since it is through it that companies are able to protect their IP from competition, once the patent is expired, it is expected that drugs with substantial market share are faced with strong generic competition (Grabowsky & Vernon 2000). As it can be seen from Figure 2 the patent-cliff is having a big impact on the sector, since 2006 the impact of patent expiration has been increasing starting with \$10bn (2% of the market at risk) total sales at risk and reaching a peak in 2012 where \$52bn (7% of the market at risk) worth of sales were considered to be at risk, which resulted in an expected loss of \$37bn that year. The scenario is expected to improve after 2016 passing from \$44bn (6% market at risk), to \$25bn (2% market at risk) in 2020.

Figure 2 - Worldwide sales at risk from patent expiration (2006-2020).

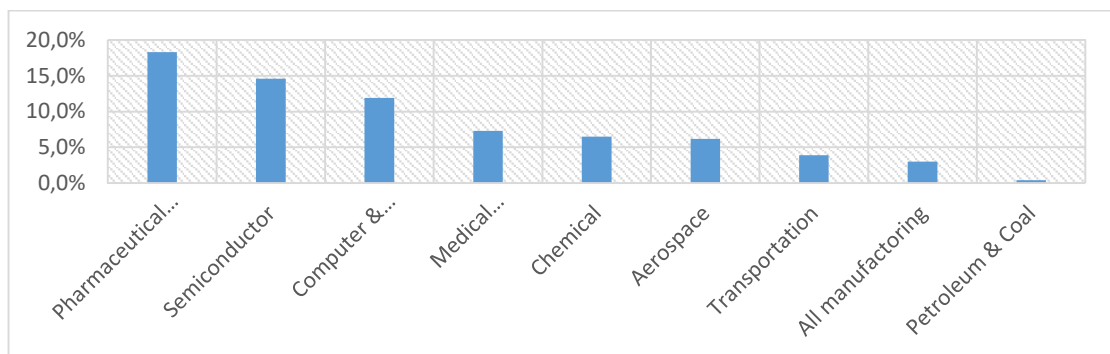


Source: EvaluatePharma, (2015), World preview 2015, outlook to 2020.

⁵ Deloitte, (2016). Global life science outlook. In: Moving forward with cautious optimism

The biopharmaceutical is one of the top performing high technology sectors, being characterized by high investments in R&D (Banerjee & Nayak 2015). We can observe (Figure 3) that between 2000 and 2012 their investment in R&D accounted for 18.3% of their sales which is the highest percentage among all the intellectual property intensive manufacturing industries. These high values are justified by the high yield returns given by the successful introduction of new drugs into the market, the way through which Pharmaceutical companies remain competitive (Banerjee & Nayak 2015).

Figure 3 - R&D as a Percentage of Sales by Industry from 2000 until 2012 (US market).



Source Pham ND; NDP Analytics. IP-intensive manufacturing industries: driving US economic growth.

In June 2000 the Human Genome Project (HGP), an international scientific research project sponsored by the governments of the United States, Canada, United Kingdom, France, Germany and China, along with numerous other private companies around the world, announced that the majority of the human genome had been sequenced, which completion was announced on April 14, 2003. The HGP was considered to be a monumental discovery for the Biopharmaceutical sector⁶, enabling a host of promising new targets and compounds to treat a range of diseases (Montazerhodjat *et al.* 2016), and generating enthusiasm in the market having the NYSE ARCA Biotech Index achieved a

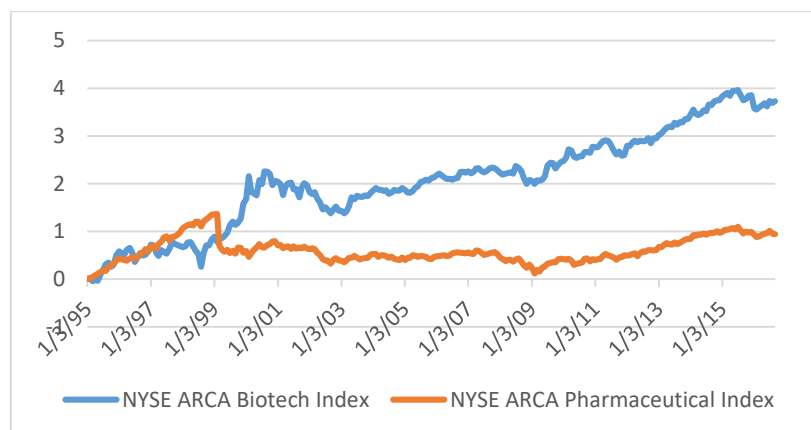
^{6,7} Lehman Brothers Equity Research: Global Life Sciences, “The Fruits of Genomics,” Lehman Brothers Equity Research, New York (January 30, 2001).

huge increase between 1998 and 2000 (Figure 4), having a record number of Biotechnology companies completed IPO in 2000⁷.

That discovery also created the need for the sector to change its practices, in order to adapt to new genomic technologies. According to ‘The Fruits of Genomics’ this period of adaptation would lead to a decade of struggle with the new biological targets that would result in lower productivity, higher failure rates, skyrocketing costs and potential lower stock returns⁸.

Since then the sector as put lot of stock in molecular-biology research and high-volume screening techniques. The number of drugs in clinical development between 2000 and 2005 increased by 40%, a huge increase when compared to the 12% increase in the 5 years prior to 2000, after the initial period going back to values of 15% between 2005 and 2010, and less than 10% from 2010 to 2015 (Leheny & Roberts 2015).

Figure 4 – Lognormal returns of NYSE ARCA Pharmaceutical Index and NYSE ARCA Biotech Index.



Source: retrieved from Yahoo finance in July 30, 2016

However, the increase of drugs in clinical development did not result in the increase productivity as measured by the approval rates of new drug applications (NDA) by the

⁸ Lehman Brothers Equity Research: Global Life Sciences, “The Fruits of Genomics,” Lehman Brothers Equity Research, New York (January 30, 2001).

United States Food and Drug Administration (FDA), which can be attributed to the lower success rates among the FDA approval process. Between 2000 and 2015, the Phase II success rate went from 50% to 25% (Leheny & Roberts 2015), having the Phase III success dropped slightly from 70% to 65% during the same period.

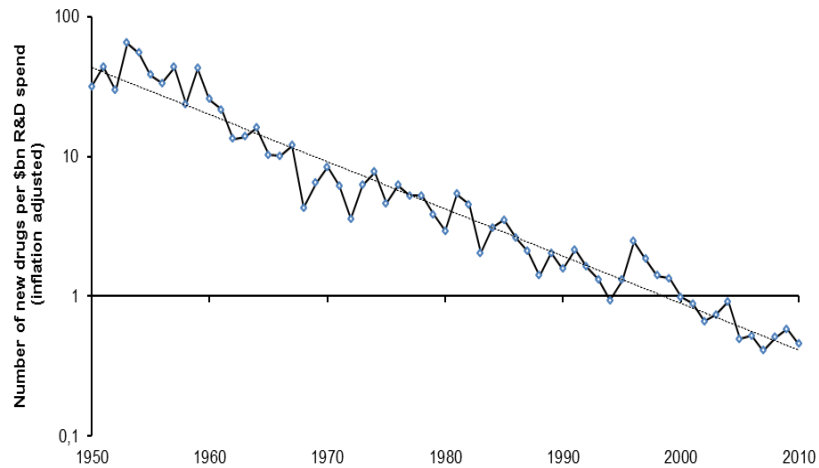
The costs of running clinical trials have been increasing since the 2000's reaching values equal to 2 up to 4 times of their initial value depending on the indication (Leheny & Roberts 2015), however this cannot be entirely attributed to bad performance in pre-clinical or clinical development, Leheny & Roberts 2015 suggest that more than half of the increase in the costs of development per patient can be attributed to the increasing requirements of the FDA for larger trials with more complex data collection. Leheny & Roberts 2015, p.52 stated that «*The skyrocketing costs of doing clinical trials have effectively offset any cost benefit that the pharmaceutical industry might have expected from the improving technologies from the HGP*».

The trend of increasing R&D costs is not new: according to Scannell *et al.* (2012) there is law called *Eroom's* according to which the number of new FDA drug approvals per \$1bn of R&D spending in the drug industry has halved approximately every nine years since 1950, in inflation-adjusted terms (Figure 5). Scannell *et al.* (2012) suggested four main reasons for the decline of the return on investment, namely: (1) new drugs for a certain disease/condition have to prove that their effects are sufficient to justify the price difference when compared to generics; (2) The difficulty of the process of testing and approval of drugs is increasing; (3) the throw money at it tendency: The high returns of R&D experienced in the past 60 years, along with pressure to be the first to launch among other reasons led to the increase of R&D budgets in a suboptimal way; (4) possible overestimation of the effectiveness of the advances in basic research and brute force screening methods of the first steps of standard discovery and preclinical research process since the probability of success of Step III has remained constant for 50 years.

The loss of return on investment as translated into the market returns of Pharmaceutical companies resulting in a loss of shareholder value of pharmaceutical companies (Figure 4). As it can be seen in Figure 6 the NYSE ARCA Pharmaceutical Index log returns during the 1990's was on a positive slope achieving good rate of return, however in the following period between 2000 and 2012 the industry went on a negative

slope reaching its lowest point in 2009, the reasons for this negative trend, can be given by the decreasing efficiency of R&D along with the patent-cliff. In the last years the sector has improved and is now again in a positive slope.

Figure 5 – Number of new drugs per \$bn R&D spent (inflation adjusted)



Source: Retrieved from Scannel *et al.* (2012)

During the same time period the NYSE ARCA Biotechnology Index (Figure 6) experienced a different path. During the 1990's they were on a volatile positive slope, but since 2003 the sector has experienced a more stable, high growth period that extends to the present

2.2 - The process of Research and Development.

The release to the market of a new medicine is the last step of a long, costly and risky process of R&D. On average a new drug will need between 10 to 15 years since its first discovery until it reaches the market (Kessel & Frank 2007).

According to the FDA a typical Drug Development Process is composed of five steps: Discovery and development, preclinical research, clinical research, FDA review and FDA post-market safety monitoring.

Step I (Discovery and development)⁹ can be separated into two sub-phases, the discovery and the development. (1) Discovery starts with the efforts of researchers to discover new drugs, starting from a sample of thousands of compounds and selecting the ones that look promising through early testing. (2) The development sub-phase will pick those compounds and proceed with experiments on them to gather information on: how they are absorbed, distributed, metabolized, and excreted; their potential benefits and mechanisms of action; the best dosage; the best way to give the drug; their side effects (toxicity); how it affects different groups of people; how it interacts with other drugs and treatments and their effectiveness as compared with similar drugs.

Step II¹⁰ (preclinical research) is the phase where the researchers find out if there is potential for serious harm and provide detailed information on dosing and toxicity levels. After testing and review of the results the decision to proceed to testing in people is done.

Step III¹¹ (Clinical Research) starts with the design of the clinical study where they decide the objectives for each one of the clinical research phases and begin the IND process, which after a successful conclusion is followed by the start of the clinical research phase studies (Figure 6).

⁹ Information retrieved from various places in FDA website, further details available at www.fda.gov.

¹⁰ Information retrieved from various places in FDA website, further details available at www.fda.gov.

¹¹ Information retrieved from various places in FDA website, further details available at www.fda.gov.

Figure 6– Clinical Research phase studies.

Phase 1	
Patients	Ranging from 20 to 100 healthy volunteers or people with the disease/condition.
Lenght of the study	Several months.
Purpose	Safety and dosage.
Phase 2	
Patients	Up to several hundred people with the disease/condition.
Lenght of the study	Several months to 2 years.
Purpose	Efficacy and side effects.
Phase 3	
Patients	From 300 to 3000 volunteers who have the disease/condition.
Lenght of the study	Ranging from 1 to 4 years.
Purpose	Efficacy and monitoring of adverse reactions.

Source: retrieved from FDA website in July 30, 2016

Step IV (FDA Review)¹² starts with the submission by the developer of a New Drug Application (NDA) which must include all information concerning the drug from preclinical trials up to phase 3 trial data with the purpose of demonstrating that the drug is safe and effective for its intended use in the population studied. After the submission is made and accepted by the FDA, the review team will have 6 to 10 months to decide the approval of the drug, during that time all the information comprised will be reviewed and supervised, routine inspections will be made, the agency will look for evidence of fabrication, manipulation, or withholding of data. All the information collected during this process will collected into an action package which will become the record for the FDA review upon which a FDA team issues a recommendation and a senior FDA official will make the decision.

Step V¹³ (FDA Post Market Safety Monitoring) refers to the continuing monitoring of the FDA of possible problems with prescription and over the counter drugs that were not identified in the previous steps and the decision to add cautions to the dosage, usage information, and other measures for more serious issues.

¹² Information retrieved from various places in FDA website, further details available at www.fda.gov.

¹³ Information retrieved from various places in FDA website, further details available at www.fda.gov.

2.3 - Investment in R&D and expansion of Drug pipelines.

After having exposed the current situation of the biopharmaceutical sector and the general composition of an R&D process, we will now make an overview of the literature surrounding the financing of the R&D for biopharmaceutical companies, which as we said before, is the way through which Pharmaceutical companies remain competitive (Banerjee & Nayak 2015), throw the introduction of new drugs into the market, which in turn requires the constant renewal of its drug pipelines (Gottinger & Umali 2008).

.First of all there are a few characteristics that differentiate the investment in R&D from other types of investments (Hall, 2002). The first characteristic that differs R&D from other types of investments is the fact that 50% or more of the spending in R&D is related to the salaries and wages of scientists and engineers, which can be seen has an intangible asset to the companies, since it is through them and their specific know-how that the company's profits will be generated in the future, and if by any chance they are fired or just leave then that intangible asset is lost to the company. Due to this, firms tend to smooth their R&D spending over time, in order to avoid having to lay off workers (Hall, 2002). The second characteristic is the uncertainty associated with the output of R&D, since only a few compounds will successfully pass all stages of development required to reach the market, meaning that for each drug to be funded and successfully reaching the market there are large amounts of funding wasted in failed attempts (Hall, 2002).

The biopharmaceutical sector has been struggling to resolve the continual renovation of their drug pipelines due to the trend of increasing costs that are required to introduce new drugs into the market, also, the adaptation to the new technologies has also been an issue, since according to Gottinger & Umali 2008: *«even the largest and best financed pharmaceutical companies cannot afford to pursue all, or even most, emerging technology platforms through in-house R&D»*. Despite these issues the cost of R&D as a function of the dollars available to the industry has experienced very little grow since the 2000's, meaning that despite the increasing of absolute costs, they have been kept stable relative to the industry revenue, being instead absorbed through the increase in drug prices

that the industry has been able to put in place (Leheny & Roberts 2015). However, as we said before, the sector is facing a reform-driven drug price control, which could mean that in the future the ability for companies to further increase the costs of its products could be limited.

As companies are faced with the need for continued renovation of their drug pipelines, they are not simply focusing on simply expanding their own in-house R&D, relying also on other alternatives like mergers and acquisitions (M&A) and strategic alliances, such as, in-licensing and co-development (Gottinger & Umali 2008), creating in that way a form of intellectual property based network specificity (Gottinger & Umali 2008).

M&A in the sector has experienced an increase as companies appear to be trying to circumvent the high uncertainty related with early stage R&D. They are searching for companies which already have done most of the research and acquire them, combining their technology, pipelines and R&D (Gottinger & Umali 2008).

In these M&A deals the acquirer is mainly the pharmaceutical sector and the acquired the biotechnology sector. This is due to the difficulty that biotech companies have in funding themselves through the long and costly R&D process, which in turn leaves them prone to be targets for the pharmaceutical sector. Biotechnology companies despite being experiencing a period of high growth and exceling in doing innovative research lack the experience in dealing with the FDA and its approval process, a process at which established pharmaceutical companies excel (Tyebjee & Hardin 2004).

When comparing between domestic and cross-borders M&A deals on the American market Banerjee *et al.*, 2015 found that domestic M&A deals tend to occur between companies which have lower ratio of R&D to sales with the objective of increasing their drug pipelines and R&D cost sharing. On the other hand, cross-border M&A deals tend to occur within companies with high ratio of R&D to sales, but have inadequate number of drugs approvals. The short term impact of these deals are similar resulting in an increase of drug approvals, however domestic M&A positive effects on drug approval tend to decrease after three years. On the other hand, cross-border deals positive effects on new drug approval last longer (at least 5 years), which result from increased market access and R&D cooperation.

Strategic alliances are a way for companies to address their financial, taking the form of cash, equity and loans, and also non-financial needs, including access to R&D, sales, marketing resources, facilities and organization (Tyebjee & Hardin 2004). These alliances offer opportunities for firms to outsource R&D efforts, allowing the creation of options on knowledge development without recurring to M&A (Gottinger & Umali 2008).

In-licensing deals are being utilized by pharmaceutical companies to license proprietary compounds or drug discovery related technologies from biotechnology companies into their drug pipelines (Rogers *et al.* 2005). These deals are deals commonly involve combinations of initial payment, milestone payments upon successful completion of the R&D stages and royalty payments during the commercialization of the product (Rogers *et al.* 2005).

Co-development deals are commonly made between small companies which have developed products up to Phase II clinical development, and a big pharmaceutical company which allows both companies to share the risk and profit from the remaining R&D process and commercialization of the product (Tyebjee & Hardin 2004). These deals have the potential to create business model options that could possibly increase profitability, enhance innovation capability, increase R&D flexibility, shorten the time to market and expand market access (Chesbrough & Schwartz 2007).

Having presented some strategies commonly used by companies to deal with the problem of renewing drug pipelines we now present some financing vehicles utilized by the sector. Even though public and private equity are among the largest and best known financing sources (Schiff & Murray 2004) in the sector we will focus on more recent financing vehicles, such as, special purpose entities (SPE), private investments in public equities, bridge financing, and royalty financing, which can help companies in the sector to finance themselves through the long and expensive process of R&D.

An SPE deal allows a company to transfer a certain project to an SPE financed by external investors, which would then contract the company to perform its R&D. the company would keep an option to repurchase the project in the future (Schiff & Murray 2004). These deals allow the parent company to share the risk of the venture, while at the

same time having the option to regain control over the drug candidate compound license (Tyebjee & Hardin 2004).

Private Investment in Public Equities (PIPE) is a method of financing used mainly by companies which are in a bad liquidity situation, with reduced ability to raise money by selling shares to the market. This process consists on a direct negotiation between a group of investors and the company to acquire stock at a discount, or debt/preferred stock which can then be converted into common stock. Through this mechanism the company would be able to fund its R&D pipeline but will be an easy target of acquisition if the R&D fails (Tyebjee & Hardin 2004).

Bridge financing are short term and very costly deals that are not desired by companies (Howell *et al.* 2003). The deals normally consist in an investor providing the companies with a loan to cover the short term financing needs of the company, the interest rates for these deals are usually pretty high and the deals also commonly contain a call and put option on an eventual acquisition. They are usually made by smaller companies following the introduction in the market of their first product which did not meet the short term expectations, resulting in reduction of stock prices and in a reduced capability of funding the market penetration of the new product and funding of its remainder drug pipeline. The deal provides the company with the desired liquidity while at the same time protecting the company from a third party acquisition (Tyebjee & Hardin 2004).

Royalty financing are deals made by companies with problems for funding research of a specific drug candidate which have reached at least Stage III or later, and which also have reduced stock prices. The deal commonly consists in an investor giving staged loans to fund the remaining R&D process and commercialization. The loan will have as collateral the future cash-flows of the drug.

Despite the increase of venture financing deals, the lack of funding for early stage R&D is severe (Montazerhodjat *et al.* 2016), Lo & Naraharisetti (2013), (p.15) stated *«In fact, as we move to the early stages of the drug discovery process – basic scientific research – the practical relevance is so speculative that the for-profit private-sector funding is virtually non-existing for such activities. This stage can only be supported by the government and not-for-profit organizations such as foundations, endowments, high net worth individuals, and patient-advocacy groups»*.

In order to address the funding gap found in the early stages of drug development Fernandez *et al* (2012) propose the creation of a Mega Fund which will provide the funding in exchange for a percentage of the future royalties or proceed from any subsequent sale of the intellectual property.

A Mega Fund as described by Fernandez *et al.* (2012) will be a combination between a mutual-fund and royalty financing, based on the creation of a single financial entity to invest in multiple projects in various states of development financed by securitized debt and equity. The Mega Fund will invest in both private and non-private companies and institutions which differentiates it from a common mutual-fund, and its assets will not be confined to drugs in late stage III or higher, as it is common for royalty financing. To face the high speculation involved in early stage R&D the Mega Fund will have to acquire a much larger set of assets to achieve the risk reduction necessary for the fund to be able to issue debt. The high amount of assets that will be available for the fund would enable it to easily relocate resources by discontinuing less promising projects in benefit of more promising ones, when compared to a common biopharmaceutical company which is commonly focused on only a few projects at a time. By concentrating all preclinical studies in a shared facility it is possible for the fund to achieve economies of scale.

The Mega Fund securitization process according to Fernandez *et al*, 2012 will consist on the creation of a Special purpose vehicle, which equity will be owned by the equity owners, with the purpose of acquiring economic rights of drugs, in exchange for upfront and milestone payments that will be used as collateral for the ‘research-backed obligation’ (RBO) that the SPV will issue and service. Additionally the SPV will also create a cash-reserve to assure the funding for development of the portfolio and also the timely repayment of the RBO. The RBO emission will be divided into tranches with different levels of risk in order to access a greater pool of investors, which will have different repayment priorities, first the senior debt followed by the junior debt and at the time of the last RBO payment is made the SPV will be liquidated being the remaining capital divided among the equity holders.

According to Fernandez *et al.* (2012) values for the Mega Fund, the probability of the fund having at least 2 successes is 99.59%, which would generate a NPV of \$24.6B

and it would enable the fund to issue nearly \$19.3B of AA-rated debt. Through the use of securitization (research backed obligations), third-party guaranties among other tools, debt capacity can even be increased. The size required to properly mitigate the risk may vary from case to case, depending on the area of research and the correspondent time probability of success and correlation among the drug compounds.

In Fagnan *et al.* (2014) the structure of the Mega Fund simulated to the specific case of orphan diseases¹⁴, diseases that affect less than 200.000 people according to US criteria, which due to their higher probability of success, lower correlation values and lower cost of development allowed the Mega Fund to significantly reduce the number of compounds and capital required. The results of the simulation suggest that smaller portfolios of drugs with just 10 compounds and \$373,75M of capital could be used as collateral for RBO transactions and achieve reasonable.

In Stein *et al.*, 2013 the structure was applied to the case of cancer, for compounds in preclinical phase that are sold once they reach Phase II, and its performance was tested with varying levels of equity, debt and also with the introduction of a third party guarantee. The results show with equal amounts of equity (\$3000M) the introduction of debt (1.250 senior and 750 junior) into the fund increased both the amount of drug compounds present in the fund that reach Phase II (63.4 to 103.1) and the average annual return on equity of the fund (7.9 to 9.1), as well as, the probability of return on equity being higher than 15% (18 to 34). The results of the Mega Fund with the same amount of capital (\$5.000M) but with varying levels of debt and equity and the introduction of a ‘no strings attached’ third party guarantee (\$1.000M) showed that the introduction of the guarantee can substantially reduce the credit losses with only an expected loss of 0.1% to 1% of the face value of the guarantee.

However Lo *et al.*, (2014) when testing the viability of the model to the Alzheimer disease case, it was found that due to the increased development costs, increased development period and less availability of compounds (64) an Alzheimer Disease Mega Fund would not be viable. The author tested the results for different levels

¹⁴ ‘The term orphan disease is used to designate diseases that affect only small numbers of individuals (so-called health orphans)’, in the USA it is defined as one that affects fewer than 200 000 individuals. J K Aronson, Chairman of the Editorial Board, British Journal of Clinical Pharmacology

of probability of success and pairwise correlation among the 64 compounds including a scenario provided by two investigators (KSK and CH) in order to achieve a simulation closest to reality, and the results were not promising being the best result an expected annual return of 8.6% with 2.8% of standard annual deviation found for a probability of success of 15% with 0% pairwise correlation, the results tend to get worse for lower probabilities of success and increasing values of pairwise correlation, and the results found for the scenario proposed by KSK CH were of an expected annual return of -14.3% with a standard annual deviation of 33.4% with a probability of 13% that no compound reaches the market.

Chapter 3 – Presentation of the Model

3.1 - Basic intuition from Lo *et al* (2014)

In this section we present the model and assumptions used by Fernandez *et al.* 2012 and Lo *et al.* 2014 for the calculation of the expected annual returns and standard deviation for an AD Mega Fund, which are used as a way to ascertain its viability by comparing the results obtained to the market benchmark.

Assuming we have an investment opportunity on a typical drug R&D program that will require yearly investments, which corresponds to k in present-value terms (i.e., at $t=0$). At maturity the investment will start to generate cash flows during the remaining life of the patent, which present value will be given by x .

The standard definition of an investment rate of return, with an initial investment of k that produces a single payoff of x is simply:

$$R = \frac{x}{k} - 1$$

In order for the return of this investment be compared with others investments which have different durations we must annualize it, which will provide us a geometric average. The annualized expected return which is given by:

$$Ra = \left(\frac{x}{k}\right)^{1/t} - 1, \text{ where } t = \text{duration}$$

Since the outcome of the investment in the R&D program is not certain we will assume that its outcome will be given accordingly with a Bernoulli trial B_i , a binary random variable that will be equal to 1 with probability p , or 0 with probability $1-p$, if the project fails or succeeds correspondently.

If we had n independently and identically distributed trials, the total number of successes will be:

$$B = \sum_{i=1}^n B_i$$

Distributed as a binomial random variable with probability distribution:

$$Prob(B = k) = \binom{n}{k} p^k (1 - p)^{n-k}, k = 1, \dots, n$$

In order to allow the outcome of the Bernoulli trials to be correlated Fernandez *et al* (2012) choose to allow pairwise dependence between B_i and B_j by assuming that associated with each Bernoulli variable B_i there is a continuous variable Z_i that is normally distributed with mean 0 and variance 1 in the following way:

$$B_i = \begin{cases} 0 & \text{if } Z_i < \alpha_i \\ 1 & \text{if } Z_i \geq \alpha_i \end{cases}$$

Where, $\alpha_i = \Phi^{-1}(1 - p_i)$ and, Φ^{-1} is the inverse of the standard normal cumulative distribution function.

If $\{Z_1, Z_2, \dots, Z_n\}$ are distributed accordingly with a multivariate standard normal distribution with covariance matrix Σ then pairwise correlation among Bernoulli trials is captured by the pairwise correlation among Z_i .

When the B_i are identically distributed with probability p and all pairwise correlations of the corresponding Z_i are identical and equal to ρ the distribution of β comes as:

$$Prob(B = k) = \binom{n}{k} q, k = 1, \dots, n$$

$$q = Prob(Z_1 > \alpha, \dots, Z_k > \alpha, Z_{k+1} \leq \alpha, \dots, Z_n \leq 0)$$

Where q is computed with respect to the multivariate standard normal distribution function with a covariance matrix given by 1 on the diagonal and ρ for all the off-diagonal elements:

$$\Sigma = \begin{pmatrix} 1 & \dots & \rho \\ \vdots & \ddots & \vdots \\ \rho & \dots & 1 \end{pmatrix}$$

The annualized expected return for n IDD trials will then be given by:

$$R = \left(\frac{Bx}{I}\right)^{1/n} - 1 \quad \text{Where, } B = \sum_{i=1}^n B_i$$

Having reached the formula for the distribution of B and the annualized return for n trials we can now derive the formula for the calculation of the expected annual return and standard deviation of annual return for a portfolio of n drug R&D programs as follow:

$$E[R_A] = \sum_{k=0}^k \left(\frac{kx}{I}\right)^{1/t} \cdot Prob(B = k) - 1$$

$$SD(R_A) = \sqrt{VAR[R_A]} = \sum_{k=0}^n \left(\frac{kx}{I}\right)^{2/t} \cdot Prob(B = k) - E^2$$

3.2 - A different approach for the viability of a Mega Fund.

The Mega Fund approach can be a solution to the research gap that has been identified for the research in the early stages of R&D. However the case of Alzheimer disease proves to be a challenge since the results found so far show that a private run AD Mega Fund doesn't have the desired expected returns and standard deviation needed to be considered viable.

The higher cost (from \$200M to \$600M) and duration (from 10 years to 13 years) of the research and development process along with the fewer possibilities available for research (150 to 64) that are correlated amongst themselves are some of the factors that may help explain the lack of investment in this area.

However the benefits arising from the discovery of new drugs in this area have the possibility to generate cost savings that could possibly overcome the problems that AD R&D faces.

Even though there is some literature lining R&D and RO, such as, Schwartz, (2004), there is not to the best of our knowledge a model that faces the point of early stage R&D financing.

On the next chapters we will present our methodology to evaluate the performance of an AD Mega Fund following a real options approach, starting with the calculations of the optimal timing for investment of the AD Mega Fund according to the parameters used by Lo *et al.* 2014, presenting afterwards a different analysis where we test the effect of the introduction of a state subsidy with the aim of stimulating the immediate start of the Mega Fund, and concluding with an analysis from the state point of view to test if the attribution of such a subsidy is in their interest.

3.2.1 - Optimum timing to invest for a Mega Fund.

Let us assume we have temporal flexibility to implement a project. In this scenario we will have interest in determining the optimal timing to invest so that we can extract the maximum value from the implementation of the project. In order to achieve our goal we will take advantage of the standard contingent claims approach defined in Dixit and Pindyck (1994).

Let $F(V)$ represent the project value-function, where V corresponds to the present value of the cash flows, weighted by the probabilities of success and pairwise correlation according to:

$$V = p(B = k) \times \sum_{i=1}^n B_i \times x$$

Let us assume that V behaves stochastically according to a geometric Brownian motion:

$$dV = \alpha V dt + \sigma V dz$$

Where $V > 0$, α correspond to the drift parameter, σ is the instantaneous volatility calculated as the projects standard deviation of annualized returns in our case taking only into account technical uncertainty, and dz is the increment of a Wiener process. Additionally, $\alpha = \mu - \delta$, where μ is the risk adjusted required rate of return and $\delta > 0$ represents the dividend-yield, or the opportunity cost for deferring.

It is assumed that the project can be implemented by investing at $t=0$ the present value of all expenses required by the Mega Fund during the entire R&D process. For simplification we will assume that all projects have equal capital requirements and that their present value is equal to k .

According to Dixit & Pindyck (1994), in order to find the optimal exercise threshold the project value function must satisfy the following ordinary differential equation (ODE):

$$\frac{1}{2}\sigma^2V^2F''(V) + (r - \delta)VF'(V) - rF(V) = 0$$

Subjecting the ODE to some conditions that must be imposed, we can obtain the appropriate solution. The general solution for this ODE will take the form:

$$C_1V^{\beta_1} + C_2V^{\beta_2}$$

Where C_1 and C_2 are arbitrary constants that need to be determined, and β_1 and β_2 are the roots of the following fundamental quadratic equation:

$$\mathcal{Q}(\beta) = \frac{1}{2}\sigma^2\beta(\beta - 1) + (r - \delta)\beta - r = 0$$

Where:

$$\beta_1 = \frac{1}{2} - \frac{r - \delta}{\sigma^2} + \sqrt{\left(-\frac{1}{2} + \frac{r - \delta}{\sigma^2}\right)^2 + \frac{2r}{\sigma^2}} > 1$$

$$\beta_2 = \frac{1}{2} - \frac{r - \delta}{\sigma^2} - \sqrt{\left(-\frac{1}{2} + \frac{r - \delta}{\sigma^2}\right)^2 + \frac{2r}{\sigma^2}} < 0$$

To determine the two constants (C_1 and C_2) we will need two conditions, additionally we also need to determine the optimal level of V for which is optimal to undertake the project (V^*). Therefore, having C_1 , C_2 and V^* as unknowns, will require three boundary conditions to complete the solution:

$$\lim_{V \rightarrow 0} F(V) = 0$$

$$\lim_{V \rightarrow V^*} F(V) = V^* - K$$

$$\lim_{V \rightarrow V^*} F'(V) = 1$$

The first condition ensures that the value of the options tends to zero as the gross project value goes to zero. The second condition ensures that for the level of V at which is optimal to invest V^* , the value of the option must equal the net value that the firm receives by undertaking the project $V^* - k$, (named ‘Value matching’). Finally, the last condition ensures that the two value function tangentially meet at $V = V^*$ (named smooth-pasting).

However if we look at the behavior of $C_2 V^{\beta_2}$ when V tends to 0 (first condition), well see that $F(V)$ tends to infinity since $\beta_2 < 0$. Therefore to respect the boundary condition C_2 must be set equal to 0.

The other two conditions are used to find the remaining unknowns, the constant C_1 and the trigger V^* such that:

$$F(V) = \begin{cases} (V^* - k) \left(\frac{V}{V^*} \right)^{\beta_1} & \text{for } V < V^* \\ V - k & \text{for } V \geq V^* \end{cases}$$

Where V^* is the trigger value that ensures the optimal decision to invest:

$$V^* = \frac{\beta_1}{\beta_1 - 1} k$$

The solution for $F(V)$ presented above has two regions, depending upon the value of V in relation to V^* . If it is not yet optimal for the firm to invest, and so $V < V^*$, the value of the investment opportunity corresponds to the value of the option to invest. On the other hand if $V \geq V^*$ the decision to invest should be taken meaning that the option to defer is worthless.

3.2.2 - Trigger for optimal timing to invest with state subsidy at $t = 0$.

In this section we use the methodology presented above and manipulate it so as to make sure that the decision to invest is made at $t = 0$. For this to be possible we will have to make sure that $V = V^*$, making the option to defer worthless. We will keep the methodology explained previously with some alterations which can be seen below.

Normally in order for the decision to invest to be considered optimal, V should exceed k by a factor of $\frac{\beta_1}{\beta_1 - 1}$ and that occurs when t is at an optimal state, such that:

$$T^* = \inf \left\{ t \geq 0 : V(t) \geq V^* = \frac{\beta_1}{\beta_1 - 1} k \right\}$$

In order for $T^* = 0$ we then proceed to change the value of the capital required to implement the project such that:

$$V = V^* = \left(\frac{\beta_1}{\beta_1 - 1} \right) (k - S^*)$$

For this to be possible we assume that the state has reached the conclusion that it is in its best interest to stimulate the Mega Fund investment immediately, being prepared to give at $t = 0$ an optimal subsidy S^* to achieve its goal.

To find the value of the optimal subsidy we solve the trigger equation in order of S^* such that:

$$S^* = k - \frac{\beta_1 - 1}{\beta_1} V$$

This optimal subsidy will then change the trigger of the decision to invest for the Mega Fund by decreasing the amount of k^* by its own value, such that:

$$V^* = V(t) = \frac{\beta_1}{\beta_1 - 1} k^* \quad \text{Where,} \quad k^* = k - S^*$$

We will then make sure that the decision to invest is always taken and the solution for $F(V)$ will only have one region:

$$F(V) = V - K^* \quad , \text{ Since } V = V^*$$

In this case the value of the investment opportunity will simply be given by its intrinsic value since the option to defer is worthless having the Mega Fund managers no reason to delay the start of the project.

Having previously assumed that it was in the state best interest to invest in the Mega Fund we now will propose a methodology to test if such an investment by the state could be considered optimal.

In order to do so function $V_s(t)$ will correspond to the present value of the cost savings that will occur if a drug is discovered by the Mega Fund weighted by the probability of at least one success in the Mega Fund which will follow a geometric Brownian motion.

In order for the project to be implemented we assume that state will have to invest a fixed amount of capital which will now be given by the value of the optimal subsidy, S^* , calculated previously. With everything else remaining the same the solution for $F(V)$ comes:

$$F(V_s) = \begin{cases} (V_s^* - S^*) \left(\frac{V_s}{V_s^*} \right)^{\beta_1} & , \text{ for } V_s < V_s^* \\ V_s - S^* & , \text{ for } V_s \geq V_s^* \end{cases}$$

Being the trigger now given by:

$$V_s^* = \frac{\beta_1}{\beta_1 - 1} S^*$$

The solution for $F(V_s)$ presented above has two regions, depending upon the value of V_s in relation to V_s^* . If it is not yet optimal for the firm to invest, i.e., $V_s < V_s^*$, the value of the investment opportunity corresponds to the value of the option to invest. On the other hand if $V_s \geq V_s^*$ the decision to invest should be taken meaning that the option to defer is worthless.

Chapter 4 - Application and analysis of the model.

On this chapter we will use the methodology presented in the previous section, apply it, and discuss the results.

We pick up on the basic assumptions used by Lo *et al.* (2014) for the creation of an AD Mega Fund composed by a portfolio of 64 drugs, each requiring an investment with present value of \$600M in year 0 (This investment is an estimation of all cost required to finance the R&D process and also takes into account early termination of drugs), that will produce from years 13 to 23 a cash-flow of \$2.000M per year if successful, which assuming a cost of capital of 10% will produce in year 13 a present value of \$12.289M.

Firstly we calculate $V(13)$ for the 13 different combinations of probabilities of success and pairwise correlations proposed by Lo *et al.* (2014), namely probabilities of success of 5%, 10% and 15% each combined with correlation of 0%, 10%, 40% and 80%, the last one named KSK-CH employ correlations calibrated qualitatively by Dr. Kenneth S. Kosik, Dr. Carole Ho, and their average, respectively, and use individually calibrated success probabilities between 5% and 15% for each of the 64 projects.

Afterwards we will calculate $V(0)$ by simply actualizing $V(13)$ at the risk adjusted discount rate for 13 periods.

The cost of the investment is simply going to be given by the cost per project multiplied by the number of projects.

Having calculated $V(0)$ for each of the scenarios we then proceed with computing the values of the Investment opportunity and option to defer for the scenarios.

The parameters used in our calculations (Table 1) were taken from Lo *et al.*, (2014) in order for a comparison between our findings and the ones from Lo *et al.*, (2014) to be possible:

Table 1 – List of parameters.

Parameter	Value
t	13
n	64
μ	10%
k	38,4

Where, t corresponds to the number of periods, n corresponds to the number of drugs in the portfolio, μ corresponds to the risk adjusted discount rate and k to the investment required.

By analyzing the results (Table 2) we can see that there isn't a single scenario where the decision to invest should be taken, i.e., $V \geq V^*$.

Table 2 – Results for RO approach of Lo *et al.* 2014.

p	ρ	σ	V(13)	V(0)	β	V^*	IV	OD
5%	0%	19,4%	39,41	11,42	4,17	50,52	-26,98	27,01
5%	10%	30,8%	39,41	11,42	2,32	67,44	-26,98	27,45
5%	40%	46,0%	29,53	8,55	1,62	100,19	-29,85	30,99
5%	80%	47,2%	10,95	3,17	1,59	103,27	-35,23	35,48
10%	0%	5,0%	78,94	22,87	45,84	39,26	-15,53	15,53
10%	10%	13,6%	77,98	22,59	7,27	44,53	-15,81	15,86
10%	40%	29,4%	59,31	17,18	2,44	65,01	-21,22	22,25
10%	80%	49,0%	16,94	4,91	1,55	108,03	-33,49	34,07
15%	0%	2,8%	117,73	34,10	143,38	38,67	-4,30	4,30
15%	10%	6,9%	117,73	34,10	24,68	40,02	-4,30	4,33
15%	40%	15,8%	93,67	27,13	5,69	46,58	-11,27	11,64
15%	80%	48,4%	28,38	8,22	1,56	106,42	-30,18	31,42
KSK-CH		33,4%	33,26	9,63	2,14	72,22	-28,77	29,22

We can see that the value of the option to defer is lowest for the scenarios with no correlation and tends to increase as we increase as we increase the correlation values, being the scenario where V is closest to V^* the one for a probability of success of 15% with no correlation where the option to defer is worth \$4,3B.

The results we get from our first analysis appear to be very similar with the ones from Lo *et al* (2014), being the only difference the fact that in their analysis the results for $p=15\%$ with $\rho=0\%$ are expected returns of 8.6%, with a return standard deviation of

2.8%, which is a ‘*risk adjusted expected return that exceeds those of most professionally managed investment funds over the past decade*’ (Lo *et al.*, 2014), and for which the decision to invest should be taken. Despite our results being different on this specific scenario, as said before, it is the one where the option to defer has the lower value amongst all scenarios analyzed.

If we look at the results from the scenario KSK-CH which is the one closest to reality we have an intrinsic value of -\$28.77B being the option to defer worth \$29,22B, confirming that the decision to invest now isn’t optimal, being in the interest of the AD Mega Fund investors to delay the investment.

We will now present our results for the value of a subsidy S^* , which assures that the decision of the private investors of the AD Mega Fund to invest is taken.

Table 3 – Results with the introduction of the subsidy.

p	ρ	σ	V(13)	V(0)	β	S^*	k- S^*	IV	OD
5%	0%	19,4%	39,41	11,42	4,17	29,72	8,68	2,74	0
5%	10%	30,8%	39,41	11,42	2,32	31,90	6,50	4,92	0
5%	40%	46,0%	29,53	8,55	1,62	35,12	3,28	5,28	0
5%	80%	47,2%	10,95	3,17	1,59	37,22	1,18	1,99	0
10%	0%	5,0%	78,94	22,87	45,84	16,03	22,37	0,50	0
10%	10%	13,6%	77,98	22,59	7,27	18,92	19,48	3,11	0
10%	40%	29,4%	59,31	17,18	2,44	28,25	10,15	7,03	0
10%	80%	49,0%	16,94	4,91	1,55	36,66	1,74	3,16	0
15%	0%	2,8%	117,73	34,10	143,38	4,54	33,86	0,24	0
15%	10%	6,9%	117,73	34,10	24,68	5,68	32,72	1,38	0
15%	40%	15,8%	93,67	27,13	5,69	16,03	22,37	4,77	0
15%	80%	48,4%	28,38	8,22	1,56	35,43	2,97	5,25	0
KSK-CH		33,4%	33,26	9,63	2,14	33,28	5,12	4,51	0

As it can be seen from Table 3 it is possible with the attribution of a subsidy to make the decision to invest optimal, the value of the option to defer is now 0 in all scenarios.

The amount of the subsidy to be given by the state is lower for scenarios without correlation and tends to increase as we increase correlation, being the scenario with the lowest subsidy the one with 15% probability of success with no correlation.

However if we look at the KSK-CH scenario we see that the value of the subsidy to be given by the state is very close to the value of the entire initial investment cost, as it happens also with the scenarios with high correlation.

These results show that a subsidy can alter the decision of the private sector to invest in the AD Mega Fund.

Now we will test if the attribution of the subsidy calculated could be considered to be in the interest of the state by comparing the cost associated with the value of the subsidy with the value of the future cost savings that would be made possible through the activity of the fund.

So, if the private sector decided to invest in an AD Mega Fund and develop a drug for AD, the state would be able to reduce its spending in Medicare and Medicaid. These savings would be cost free since the state would have no costs associated.

As it was proven before, as is, the AD Mega Fund is not a viable investment which means that the benefits that would arise from the discovery of a new drug will only be possible with state intervention.

So, as we proved in the previous section if the state intervene and attribute a subsidy the decision to invest by the private AD Mega Fund will be taken, and the benefits in the form of cost savings will be also made possible.

In order to calculate the value of such benefits we will use the projection given by the American Alzheimer association for cost savings in Medicaid and Medicare, that would occur if one of two drugs were discovered, a drug that delays the onset of AD (T2), or a drug that slows the progression of AD.

Bellow (Table 4) we can see the present values of the cost savings according to 3 different time horizons (10, 20, and 30 years) that are expected to occur according American Alzheimer Association if T2 or T3 occur:

Table 4 – Cost savings projection according to the American Alzheimer Association retrieved from Lo *et al.* (2014).

Trajectory	10 year 2015-2025	20 year 2015-2035	30 year 2015-2045
T2	208	804	1513
T3	156	468	813

For this analysis we will consider the investment cost k to be equal to the subsidy (since the AA values are in constant 2010 dollars the value of the subsidy must be converted) and the V will be the present value of the savings in Medicaid and Medicare pondered by the probability of at least one-hit that would be realized if a new drug is discovered (Lo *et al.* 2014).

We will test the performance of the model for each trajectory independently. Assuming in each analysis that the first drug discovered by the firm will always lead to the cost-savings expressed in the Table above.

This way we can compute the value of the investment opportunity for the state for each scenario and time horizon (Annex 1).

The results we can observe from T2 with a 10 year horizon are quite promising. For a 5% probability of success with no correlation we get a value of \$28,27B for the investment opportunity, having the option to defer a value of 0. However as we increase correlation by 10 %, the option to defer becomes valuable. For higher probabilities of success (10% and 15%) the value of the option to defer is kept at 0, only gaining value for extreme correlation values. However the option to defer for KSK-CH is still valuable. For T2 with a 20 year horizon the results keep improving having now only two scenarios where the option to defer is valuable, which are the ones for extreme correlation values with 5% and 10% probability of success. For T2 with a 30 year horizons the option to defer as a value of 0 for all scenarios.

For the T3 trajectory the results are quite similar to the one observed in T2. For a 10 year horizon the option to defer still has value of \$1.21B for a 10% probability of success and 40% correlation, remaining all scenarios similar to the ones from T2. For a 20 year horizon the option to defer still has value for scenarios of 5% and 15%

probabilities of success with correlations of 40% and 80% respectively. And for the 30 year horizon we only get positive values for the option to defer for extreme correlation values with 5% and 10% probabilities of success.

Overall the results obtained tend to improve as we increase the horizon. At a horizon of 10-years for T2 there are 7 scenarios where the decision to invest is optimal, for T3 this number goes down to 6, however neither in T2 or T3 the scenario proposed by KSK-CH is viable. When the horizon is set at 20 years more scenarios are made viable, more precisely 4 for T2 and 2 for T3, among those is the scenario KSK-CH.

For the 30-year horizon the decision to invest should be taken for all T2 scenarios, and for T3 there are only two scenarios where the decision to invest isn't optimal. These results show that a subsidy can alter the decision of the private sector to invest in the AD Mega Fund. Despite the high values the subsidy would have to take (up to 93% of Investment cost) it will still be optimal for the state to invest since the benefits that would arise from the discovery are such that decision to give the subsidy will always be taken if we take into account a 20 year horizon.

However their analysis of the scenarios presented by the American Alzheimer Association projected costs related with Alzheimer disease shows that the state would incur in significant savings if some drug to AD was discovered. So, on the case the investor of the AD Mega Fund do decide to proceed with the investment they will be creating value for themselves and the state, however the state will earn those benefits without incurring in any risk or capital commitment. But since the Mega Fund investors are assumed to be rational investors, the decision to invest in the AD Mega Fund will not be taken and by consequence the state will not receive the benefits from it.

Chapter 5 - Conclusions

On this dissertation we have presented the biopharmaceutical sector along, the process of R&D along with the methods used by the sector to expand and finance their drug pipelines, which is the way through which they remain competitive. Having a gap in the sectors financing, been identified, more precisely for the early stages of R&D, we presented literature that has proposed a solution to close that gap, focusing on the Mega Fund.

However, when applying that structure to the specific case of AD it was found that due to the increased development costs, increased development period and less availability of compounds an Alzheimer Disease Mega Fund would not be viable through private intervention alone.

By applying our RO approach to the AD Mega Fund we found that our results were similar to the ones from Lo *et al.* 2014, which lead us to try and present an different approach for the viability of the AD Mega Fund. The introduction of the state could be interesting since, as is was exposed, the introduction of new drugs to treat AD would lead to huge cost savings in their part. Even though these cost savings could normaly be accomplished through private investment, in the specific case of AD, as it was exposed such would not be possible, and so we tested the impact that a state subsidy could generate. According to our results the atribution by the state of a subsidy could in fact make the decision to invest immediately optimal for the Mega Fund. Despite the high values that such a subsidy would have to take, the cost savings in a 20 and 30 year horizon, that the state would be able to attain are enough to make the decision to give the subsidy optimal for the state in the scenario that is closest to reality (KSK-CH) and also in almost all other scenarios presented.

It would be interesting in the future to explore ways in which the atribution of such subsidies could be integrated with the state efforts to control drug costs, possibly with the introduction of a clause in which the atribution of such subsidies would not only be justified by the cost savings that the state would be able to attain directly, but also as an incentive to the decrease in drug costs, created as a result of the atribution of the subsidy, for the population.

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Annex 1

Table A1 – Results for the state point of view subsidy under T3.

T3		Slowed Progression - 10 years							Slowed Progression - 20 years							Slowed Progression - 30 years						
p	ρ	S*	σ	V(0)	β	V*	IV	OD	S*	σ	V(0)	β	V*	IV	OD	S*	σ	V(0)	β	V*	IV	OD
5%	0%	29,72	21,61%	43,47	3,58	41,24	13,75	0,00	29,72	23,54%	130,41	3,19	43,27	100,69	0,00	29,72	24,55%	226,55	3,03	44,39	196,82	0,00
5%	10%	31,90	34,51%	40,49	2,07	61,78	8,59	3,88	31,90	37,54%	121,46	1,91	66,90	89,56	0,00	31,90	39,15%	211,01	1,84	69,78	179,11	0,00
5%	40%	35,12	52,09%	30,95	1,49	106,63	-4,17	15,47	35,12	56,70%	92,86	1,42	119,13	57,74	1,27	35,12	59,10%	161,32	1,39	126,05	126,19	0,00
5%	80%	37,22	54,75%	18,17	1,45	120,52	-19,06	24,45	37,22	59,53%	54,50	1,38	134,94	17,28	10,66	37,22	62,13%	94,67	1,35	143,22	57,45	3,14
10%	0%	16,03	4,04%	45,13	69,44	16,27	29,10	0,00	16,03	4,47%	135,40	57,07	16,32	119,37	0,00	16,03	4,68%	235,22	52,12	16,35	219,19	0,00
10%	10%	18,92	14,18%	44,51	6,78	22,20	25,59	0,00	18,92	15,44%	133,53	5,90	22,78	114,61	0,00	18,92	16,07%	231,96	5,54	23,09	213,04	0,00
10%	40%	28,25	32,19%	41,26	2,22	51,46	13,00	1,21	28,25	35,04%	123,77	2,04	55,48	95,52	0,00	28,25	36,57%	215,01	1,96	57,76	186,76	0,00
10%	80%	36,66	55,71%	21,01	1,43	121,45	-15,64	22,52	36,66	60,70%	63,04	1,37	136,52	26,38	8,34	36,66	63,30%	109,51	1,34	144,85	72,85	1,55
15%	0%	4,54	0,70%	45,19	2252,27	4,54	40,65	0,00	4,54	0,82%	135,56	1655,08	4,54	131,02	0,00	4,54	0,82%	235,49	1655,08	4,54	230,95	0,00
15%	10%	5,68	5,99%	45,10	32,30	5,86	39,42	0,00	5,68	6,57%	135,29	27,10	5,90	129,61	0,00	5,68	6,80%	235,03	25,38	5,91	229,35	0,00
15%	40%	16,03	16,49%	44,33	5,32	19,74	28,29	0,00	16,03	17,87%	132,99	4,70	20,36	116,95	0,00	16,03	18,62%	231,02	4,43	20,71	214,99	0,00
15%	80%	35,43	54,45%	28,02	1,45	113,93	-7,42	17,66	35,43	59,26%	84,05	1,38	127,64	48,61	3,10	35,43	61,76%	146,01	1,36	135,22	110,57	0,00
KSK-CH		33,28	37,82%	39,31	1,90	70,30	6,04	6,24	33,28	41,24%	117,94	1,76	76,85	84,66	0,00	33,28	43,05%	204,88	1,70	80,53	171,60	0,00

Table A2– Results for the state point of view subsidy under T2.

T2		Delayed Onset - 10 years							Delayed Onset - 20 years							Delayed Onset - 30 years						
p	ρ	S*	σ	V(0)	β	V*	IV	OD	S*	σ	V(0)	β	V*	IV	OD	S*	σ	V(0)	β	V*	IV	OD
5%	0%	29,72	22,12%	57,99	3,47	41,76	28,24	0,00	29,72	24,45%	224,04	3,04	44,28	194,32	0,00	29,72	25,67%	421,61	2,86	45,67	391,88	0,00
5%	10%	31,90	35,32%	53,98	2,02	63,11	22,08	0,67	31,90	39,15%	208,67	1,84	69,78	176,77	0,00	31,90	41,07%	392,68	1,77	73,35	360,78	0,00
5%	40%	35,12	53,29%	41,27	1,47	109,79	6,15	11,57	35,12	59,10%	159,53	1,39	126,05	124,41	0,00	35,12	62,00%	300,21	1,35	134,77	265,09	0,00
5%	80%	37,22	55,94%	24,22	1,43	124,01	-13,00	21,41	37,22	62,13%	93,62	1,35	143,22	56,40	3,28	37,22	65,22%	176,18	1,32	153,55	138,96	0,00
10%	0%	16,03	4,15%	60,18	65,99	16,28	44,15	0,00	16,03	4,68%	232,62	52,12	16,35	216,58	0,00	16,03	4,89%	437,75	47,79	16,37	421,71	0,00
10%	10%	18,92	14,50%	59,35	6,54	22,34	40,42	0,00	18,92	16,07%	229,40	5,54	23,09	210,47	0,00	18,92	16,81%	431,69	5,17	23,46	412,77	0,00
10%	40%	28,25	32,90%	55,01	2,17	52,44	26,76	0,00	28,25	36,57%	212,63	1,96	57,76	184,38	0,00	28,25	38,40%	400,13	1,87	60,60	371,88	0,00
10%	80%	36,66	57,01%	28,02	1,41	125,25	-8,64	19,30	36,66	63,30%	108,29	1,34	144,85	71,64	1,66	36,66	66,39%	203,79	1,31	155,20	167,14	0,00
15%	0%	4,54	0,70%	60,25	2252,27	4,54	55,71	0,00	4,54	0,82%	232,88	1655,08	4,54	228,35	0,00	4,54	0,82%	438,25	1655,08	4,54	433,71	0,00
15%	10%	5,68	6,11%	60,13	31,14	5,87	54,45	0,00	5,68	6,80%	232,42	25,38	5,91	226,74	0,00	5,68	7,14%	437,39	23,10	5,94	431,71	0,00
15%	40%	16,03	16,81%	59,11	5,17	19,88	43,07	0,00	16,03	18,62%	228,47	4,43	20,71	212,43	0,00	16,03	19,58%	429,94	4,11	21,18	413,90	0,00
15%	80%	35,43	55,66%	37,36	1,43	117,25	1,92	13,96	35,43	61,76%	144,39	1,36	135,22	108,96	0,00	35,43	64,77%	271,72	1,32	144,71	236,29	0,00
KSK-CH		33,28	38,73%	52,42	1,86	71,98	19,14	2,32	33,28	42,95%	202,61	1,71	80,32	169,34	0,00	33,28	45,06%	381,29	1,65	84,78	348,01	0,00